Glycated Haemoglobin and Cardiovascular Risk Factors in Chinese Subjects with Normal Glucose Tolerance

G.T.C. Ko*[1], J.C.N. Chan[1], J. Woo[1], E. Lau[2], V.T.F. Yeung,[1], C.-C. Chow,[1], J.K.Y. Li[1], W.-Y. So[1], W.-B. Chan,[1], C.S. Cockram[1]

[1]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong*
[2]*Department of Community and Family Medicine, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong*

Increased plasma glucose concentration is a predictive factor for mortality in both diabetic and non-diabetic subjects. Although glycated haemoglobin (HbA_{1c}) is a useful index of mean blood glucose concentrations over the preceding 1 to 3 months, there are few data regarding its relationship to cardiovascular risk. We have examined the relationship between HbA_{1c} and cardiovascular risk factors in 1280 subjects with normal glucose tolerance. Based on HbA_{1c} tertiles (tertile 1: *n* = 427, 262 men and 165 women, HbA_{1c} level: 2.9–4.7 % in men and 3.2–4.2 % in women; tertile 2: *n* = 426, 261 men and 165 women, HbA_{1c} level: 4.7–5.1 % in men and 4.2–4.6 % in women; tertile 3: *n* = 427, 262 men and 165 women, HbA_{1c} level: 5.1–6.7 % in men and 4.6–6.9 % in women), increasing HbA_{1c} was associated with increasing age, blood pressure, waist–hip ratio, fasting and 2-h plasma glucose, 2-h insulin, cholesterol, low-density lipoprotein cholesterol, apolipoprotein B and urate concentrations. When age and sex were included as covariates, increasing HbA_{1c} remained associated with increasing fasting and 2-h plasma glucose, 2-h insulin, total cholesterol, and low-density lipoprotein cholesterol concentrations. These findings emphasize the importance of hyperglycaemia, as reflected by HbA_{1c}, as a continuum in the evaluation of cardiovascular risk. Furthermore, these findings support the hypothesis that cardiovascular disease risk commences with rising glucose concentrations before 'conventionally-defined' glucose intolerance occurs. © 1998 John Wiley & Sons, Ltd.

Diabet. Med. **15: 573–578 (1998)**

KEY WORDS **glycated haemoglobin; cardiovascular risk factors; Chinese; normal glucose tolerance**

Received 21 January 1997; revised 20 August 1997; accepted 8 February 1998

Introduction

Cardiovascular disease (CVD) is a major cause of death and morbidity in both general and diabetic populations.[1–3] The prevalence rates of coronary artery disease, cerebrovascular accident and peripheral vascular disease are two to five times higher in diabetic compared to non-diabetic subjects.[2–5] Epidemiological studies have shown an association between the prevalence of CVD and glycated haemoglobin (HbA_{1c}) in diabetic women.[6] In a 3-year prospective study, baseline HbA_{1c} levels predicted both coronary heart disease (CHD) death and all CHD events in 229 elderly patients with Type 2 diabetes mellitus (DM).[7] Furthermore, there was a dose–response relationship between HbA_{1c} and the risk of CHD such that in subjects with HbA_{1c} greater than 7.9 %, the incidence of CHD mortality and all CHD events were highest (12.5 % and 21.0 %, respectively). This is in contrast to the respective mortality rates of 5 % and 13 % in patients with HbA_{1c} values between 6.0 % and 7.9 %. In patients with HbA_{1c} values less than 6.0 %, the respective rates were 1.5 % and 8 %.[7] In post-myocardial infarction patients, optimal glycaemic control was associated with reduced mortality within 1 year.[8]

Recently, Gerstein and Yusuf have proposed a new term, dysglycaemia, to define the range of glucose concentrations associated with an increased risk of CVD.[9] They suggested that lowering plasma glucose concentrations in people who have normal glucose tolerance might help to prevent CVD. Other studies have also shown that an increased plasma glucose concentration was predictive for mortality in both diabetic[10] and non-diabetic subjects.[11]

We have examined HbA_{1c} and its relationship with cardiovascular risk factors in 1280 subjects who had normal glucose tolerance as defined by conventional

*Correspondence to: Dr G.T.C. Ko, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong

CCC 0742–3071/98/070573–06$17.50

World Health Organization (WHO) criteria.[12] Although HbA_{1c} is a useful index reflecting mean blood glucose concentrations over the preceding 1 to 3 months,[13] there is a paucity of data regarding its relationship to cardiovascular risk. We examine these associations in a survey of glucose intolerance and lipid abnormality in a Hong Kong Chinese working population.[14] The prevalence data have been previously published.[14] The present report concentrates on the associations between cardiovascular risk factors and HbA_{1c} in subjects with normal glucose tolerance.

Patients and Methods

In this population-based study involving 1513 participants, HbA_{1c} results were available in 1435 subjects and form the basis for the present analysis. The methodology of the survey has been described.[14] In brief, we conducted a joint survey for the prevalence of diabetes and lipoprotein disorders in a Hong Kong Chinese working population aged between 30 and 65 years in 1990. All employees from two worksites of a major public utility company and a regional hospital were invited to participate. On the study day, all subjects attended their worksites after an overnight fast. Demographic data including blood pressure, body weight, height, waist and hip circumferences were measured. Body mass index was calculated as weight (kg) divided by the square of the height (m). Waist-to-hip ratio was used as an index of central adiposity.[15]

Blood was taken after a 12 h fast for measurement of HbA_{1c}, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein AI, and apolipoprotein B. All subjects underwent a 75 g oral glucose tolerance test (OGTT). Fasting and 2-h plasma glucose and insulin were measured during the OGTT. A random spot urine sample was collected for the measurement of albumin concentration. The laboratory assays have been described.[14] In short, plasma glucose was measured by a glucose oxidase method (Diagnostic Chemicals Ltd, Canada). The intra-assay coefficient of variation (CV) of glucose was 2 % at 6.6 mmol l^{-1}. HbA_{1c} was measured by an automated ion-exchange chromatographic method (Bio-Rad Laboratory, Hercules, CA, USA). Inter- and intra-assay CV for HbA_{1c} was $\leq$ 3.1 % at values below 8.5 %. The WHO criteria were used for the diagnosis of diabetes and impaired glucose tolerance (IGT).[12]

Statistical Analysis

Statistical analysis was performed using the SPSS (version 6.0) software on an IBM compatible computer. Plasma triglyceride insulin concentrations, and urine albumin concentration were logarithmically transformed due to skewed distributions. All results are expressed as mean $\pm$ SD or geometric mean $\times/\div$ antilog SD where appropriate. The analysis of covariance (ANCOVA) was used for between group comparisons with age and sex or haemoglobin levels as covariates where appropriate. The subjects were stratified into tertiles according to HbA_{1c} levels and their relationships with various cardiovascular risk factors were analysed (tertile 1: n = 427, 262 men and 165 women, HbA_{1c} level: 2.9–4.7 % in men and 3.2–4.2 % in women; tertile 2: n = 426, 261 men and 165 women, HbA_{1c} level: 4.7–5.1 % in men and 4.2–4.6 % in women; tertile 3: n = 427, 262 men and 165 women, HbA_{1c} level: 5.1–6.7 % in men and 4.6–6.9 % in women). A p value <0.05 (two-tailed) was considered to be significant. Multivariate analysis using fasting and 2-h plasma glucose, glycated haemoglobin, age, and male sex as independent variables were performed. The standardized regression coefficients (β) were examined to assess the relationships between the independent variables and various cardiovascular risk factors.

Results

Of the 1435 subjects included in the present analysis, 1280 had normal glucose tolerance, 106 had impaired glucose tolrance (IGT), and 49 had diabetes. After excluding all subjects with glucose intolerance (n = 155), we examined the clinical and biochemical characteristics in the remaining subjects (785 (61.3 %) mean and 495 (38.7 %) women). Men were younger, had higher blood pressure, waist–hip ratio, HbA_{1c}, plasma cholesterol, triglyceride, low-density lipoprotein, apolipoprotein B, urate, and haemoglobin concentrations than women. In addition, men had lower plasma glucose, fasting insulin, high-density lipoprotein, apolipoprotein AI, and urine albumin concentrations (Table 1). Apart from fasting plasma glucose, all these differences remained significant after adjustment for age and haemoglobin concentrations.

The subjects were stratified into tertiles according to HbA_{1c} levels. Increased HbA_{1c} was positively associated with age, blood pressure, waist–hip ratio, fasting, and 2-h plasma glucose, 2-h insulin, plasma cholesterol, low-density lipoprotein, apolipoprotein B, and urate concentrations (Table 2). Although the p-value for apolipoprotein AI was <0.05, a linear trend was not seen. When age and sex were included as covariates, higher HbA_{1c} values remained associated with increased fasting and 2-h plasma glucose, 2-h insulin, plasma total cholesterol and low-density lipoprotein cholesterol concentrations.

On multivariate analysis using age, male sex, HbA_{1c}, fasting and 2-h plasma glucose as independent variables, we found that age, male sex and 2-h plasma glucose were independently associated with most of the cardiovascular risk factors, namely blood pressure, obesity, lipid parameters, and urate. HbA_{1c} was independently associated with total cholesterol and low-density lipoprotein with a standardized regression coefficient higher than that of fasting plasma glucose but less than that of 2-h plasma glucose (Table 3).

Table 1. Characteristics of men and women with normal glucose tolerance tests

Variable	Total (n = 1280)	Men (n = 785)	Women (n = 495)	p-value	p-value with age and haemoglobin levels as covariates
Age (year)	36.7 ± 8.9	35.9 ± 8.9	38.0 ± 8.9	<0.001	–
Systolic BP (mmHg)	118 ± 15	123 ± 13	110 ± 15	<0.001	<0.001
Diastolic BP (mmHg)	75 ± 10	78 ± 9	70 ± 10	<0.001	<0.001
WHR	0.84 ± 0.07	0.87 ± 0.06	0.80 ± 0.06	<0.001	<0.001
BMI (kg m^{-2})	23.1 ± 3.1	23.2 ± 2.9	22.9 ± 3.3	0.180	0.519
Fasting PG (mmol l^{-1})	4.8 ± 0.5	4.7 ± 0.4	4.8 ± 0.6	0.001	0.368
2-h PG (mmol l^{-1})	5.1 ± 1.1	5.0 ± 1.2	5.4 ± 1.1	<0.001	<0.001
HbA_{1c} (%)	4.7 ± 0.6	4.9 ± 0.6	4.5 ± 0.6	<0.001	<0.001
Fasting insulin (μU ml^{-1})[a]	7.2 ×/÷ 1.6	6.9 ×/÷ 1.6	7.8 ×/÷ 1.7	<0.001	<0.001
2-h insulin (μU ml^{-1})[a]	36.3 ×/÷ 2.1	36.3 ×/÷ 2.1	37.2 ×/÷ 2.2	0.923	0.002
TC (mmol l^{-1})	5.02 ± 0.94	5.20 ± 1.00	4.73 ± 0.83	<0.001	<0.001
TG (mmol l^{-1})[a]	0.93 ×/÷ 1.74	1.10 ×/÷ 1.70	0.71 ×/÷ 1.70	<0.001	<0.001
HDL (mmol l^{-1})	1.36 ± 0.36	1.25 ± 0.31	1.54 ± 0.37	<0.001	<0.001
LDL (mmol l^{-1})	3.23 ± 0.88	3.37 ± 0.91	3.00 ± 0.78	<0.001	<0.001
Apolipoprotein AI (g l^{-1})	134.2 ± 28.8	124.6 ± 24.7	149.6 ± 28.2	<0.001	<0.001
Apolipoprotein B (g l^{-1})	76.8 ± 19.6	79.5 ± 19.5	72.6 ± 19.1	<0.001	0.002
Urate (mmol l^{-1})	0.36 ± 0.09	0.39 ± 0.09	0.31 ± 0.06	<0.001	<0.001
Spot urine albumin[a] (mg l^{-1})	3.6 ×/÷ 3.0	3.1 ×/÷ 3.0	4.5 ×/÷ 3.0	<0.001	<0.001
Haemoglobin (g dl^{-1})	14.3 ± 1.5	15.1 ± 1.1	13.0 ± 1.1	<0.001	–

[a]Geometric mean ×/÷ anti-logarithmic SD.
BP, blood pressure; WHR, waist–hip ratio; BMI, body mass index; PG, plasma glucose; HbA_{1c}, glycated haemoglobin; TC, total cholesterol; TG, fasting triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. Comparison for major cardiovascular risk factors among the three tertiles of HbA_{1c} levels in subjects with normal glucose tolerance

Variable	Tertile 1 (n = 427; 262 men, 165 women)	Tertile 2 (n = 426; 261 men, 165 women)	Tertile 3 (n = 427; 262 men, 165 women)	p-value for trend (ANOVA)	p-value with age and sex as covariates
Age	34.7 ± 8.5	36.4 ± 7.9	39.1 ± 9.8	<0.001	–
Systolic BP (mmHg)	116 ± 15	117 ± 14	120 ± 16	0.004	0.177
Diastolic BP (mmHg)	74 ± 10	75 ± 10	76 ± 11	0.008	0.384
WHR	0.83 ± 0.07	0.84 ± 0.07	0.85 ± 0.07	0.002	0.240
BMI (kg m^{-2})	23.0 ± 3.0	22.9 ± 3.0	23.3 ± 3.2	0.166	0.634
Fasting PG (mmol l^{-1})	4.7 ± 0.5	4.8 ± 0.5	4.9 ± 0.5	<0.001	<0.001
2-h PG (mmol l^{-1})	4.9 ± 1.1	5.2 ± 1.1	5.3 ± 1.2	<0.001	<0.001
HbA_{1c} (%)	4.2 ± 0.4	4.7 ± 0.3	5.3 ± 0.5	<0.001	<0.001
Fasting insulin (μU ml^{-1})[a]	7.2 ×/÷ 1.6	7.3 ×/÷ 1.6	7.4 ×/÷ 1.6	0.834	0.973
2-h insulin (μU ml^{-1})[a]	36.6 ×/÷ 2.2	38.0 ×/÷ 2.1	38.9 ×/÷ 2.2	0.011	0.025
TC (mmol l^{-1})	4.87 ± 0.94	5.06 ± 0.89	5.13 ± 0.98	<0.001	0.019
TG* (mmol l^{-1})	0.91 ×/÷ 1.80	0.90 ×/÷ 1.73	0.97 ×/÷ 1.74	0.141	0.516
HDL (mmol l^{-1})	1.37 ± 0.37	1.35 ± 0.34	1.36 ± 0.38	0.812	0.866
LDL (mmol l^{-1})	3.09 ± 0.89	3.28 ± 0.85	3.33 ± 0.89	<0.001	0.014
Apolipoprotein AI (g l^{-1})	133.8 ± 29.1	131.8 ± 28.1	136.9 ± 28.9	0.035	0.041
Apolipoprotein B (g l^{-1})	74.9 ± 29.1	76.9 ± 19.0	78.7 ± 20.6	0.020	0.662
Urate (mmol l^{-1})	0.35 ± 0.07	0.36 ± 0.12	0.36 ± 0.08	0.041	0.062
Spot urine albumin[a] (mg l^{-1})	3.5 ×/÷ 3.0	3.6 ×/÷ 3.1	3.6 ×/÷ 3.0	0.855	0.878
Haemoglobin (g dl^{-1})	14.3 ± 1.5	14.3 ± 1.5	14.2 ± 1.5	0.166	0.212

[a]Geometric mean ×/÷ anti-logarithmic SD.
BP, blood pressure; WHR, waist–hip ratio; BMI, body mass index; PG, plasma glucose; HbA_{1c}, glycated haemoglobin; TC, total cholesterol; TG, fasting triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
HbA_{1c} level: tertile 1: 2.9–4.7 % in men and 3.2–4.2 % in women; tertile 2: 4.7–5.1 % in men and 4.2–4.6 % in women; tertile 3: 5.1–6.7 % in men and 4.6–6.9 % in women.

Discussion

Existing epidemiological data have shown that diabetic subjects have increased cardiovascular risk compared to age- and sex-matched non-diabetic subjects.[2–5,7,8,10,11] However, the relationships between hyperglycaemia and atherosclerosis remain controversial. In Type 1 DM, there is no relationship between HbA_{1c} and the intimal-medial thickness of the common carotid artery as measured by ultrasonography.[16] In Type 2 DM, although the mean intimal-medial thickness of both common carotid arteries as measured by similar methodology was found to be higher in diabetic patients compared to age- and sex-matched controls, multiple regression analysis

Table 3. Multivariate analysis using fasting plasma glucose, 2-h plasma glucose, glycated haemoglobin, age and male sex as independent variables to assess their relationships with various cardiovascular risk factors

	Fasting plasma glucose	2-h plasma glucose	Glycated haemoglobin	Age	Male sex	Analysis of variance		
	β	β	β	β	β	R^2	F	*p*
SBP	0.070[b] (0.018, 0.122)	0.092[c] (0.040, 0.144)	0.016 (−0.035, 0.067)	0.216[c] (0.165, 0.267)	0.457[c] (0.404, 0.510)	0.252	87.3	<0.001
DBP	0.050 (−0.004, 0.103)	0.074[b] (0.021, 0.127)	0.007 (−0.047, 0.061)	0.236[c] (0.184, 0.288)	0.423[c] (0.371, 0.470)	0.222	74.1	<0.001
WHR	0.048[a] (0.001, 0.096)	0.119[c] (0.007, 0.161)	0.031 (−0.018, 0.075)	0.284[c] (0.235, 0.321)	0.543[c] (0.475, 0.584)	0.371	152.0	<0.001
BMI	0.112[c] (0.055, 0.170)	0.155[c] (0.098, 0.212)	−0.013 (−0.072, 0.045)	0.166[c] (0.111, 0.221)	0.999[c] (0.041, 0.163)	0.091	26.6	<0.001
FI	0.116[c] (0.058, 0.175)	0.204[c] (0.146, 0.259)	−0.011 (−0.073, 0.052)	−0.013 (−0.069, 0.043)	−0.077[a] (−0.135, −0.018)	0.080	22.9	<0.001
2h-1	−0.054[a] (−0.107, −0.002)	0.558[c] (0.510, 0.610)	0.027 (−0.025, 0.079)	−0.045 (−0.093, 0.005)	0.066[a] (0.014, 0.117)	0.279	98.5	<0.001
TC	−0.068[a] (−0.124, −0.012)	0.106[c] (0.052, 0.170)	0.071[a] (0.013, 0.128)	0.218[c] (0.161, 0.275)	0.250[c] (0.185, 0.300)	0.124	37.1	<0.001
TG	0.001 (−0.051, 0.052)	0.184[c] (0.132, 0.236)	0.017 (−0.037, 0.072)	0.158[c] (0.119, 0.229)	0.414[c] (0.373, 0.497)	0.206	67.3	<0.001
HDL	−0.076[b] (−0.131, −0.021)	−0.110[c] (−0.163, −0.057)	−0.005 (−0.062, 0.052)	−0.008 (−0.067, 0.053)	−0.412[c] (−0.481, −0.371)	0.171	53.6	<0.001
LDL	−0.043 (−0.101, 0.015)	0.107[c] (0.052, 0.164)	0.073[a] (0.015, 0.131)	0.203[c] (0.147, 0.264)	0.2114[c] (0.161, 0.268)	0.104	30.5	<0.001
ApoA	−0.018 (−0.074, 0.038)	0.009 (−0.045, 0.063)	0.023 (−0.032, 0.078)	0.056[a] (0.003, 0.109)	−0.424[c] (−0.482, −0.373)	0.178	56.1	<0.001
ApoB	−0.023 (−0.079, 0.033)	0.135[c] (0.079, 0.194)	0.039 (−0.019, 0.097)	0.252[c] (0.195, 0.306)	0.205[c] (0.154, 0.282)	0.120	35.7	<0.001
Urate	0.026 (−0.028, 0.079)	0.065[a] (0.011, 0.118)	0.041 (−0.013, 0.095)	0.063[a] (0.011, 0.118)	0.452[c] (0.398, 0.511)	0.212	69.7	<0.001
Ualb	0.073[a] (0.014, 0.132)	0.068[a] (0.009, 0.127)	0.006 (−0.052, 0.064)	−0.021 (−0.079, 0.037)	−0.150[c] (−0.210, 0.090)	0.035	10.4	<0.001
Hb	−0.046[a] (−0.090, −0.002)	0.042 (−0.001, 0.086)	0.027 (−0.017, 0.071)	−0.084[c] (−0.126, −0.042)	0.666[c] (0.632, 0.733)	0.474	230.3	<0.001

β, standardized regression coefficient (95 % confidence interval); SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist–hip ratio; FI, fasting insulin; 2h-I, 2-h insulin; TC, total cholesterol; TG, fasting triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ApoA, apolipoprotein-A1; ApoB, apolipoprotein-B; Ualb, urine albumin concentration; Hb, haemoglobin.
p-values: [a]<0.05, [b]<0.01, [c]<0.001.

did not show any correlation between HbA_1 and the arterial intimal-medial thickness.[17] However, others have reported an independent relationship between the prevalence of large vessel disease and HbA_1 values in diabetic subjects.[18] In prospective studies involving subjects with both Type 1 and Type 2 DM, the baseline HbA_1 was found to be a good predictor for the subsequent development of vascular complications and CHD.[10,19] Other workers have also shown a reduction in plasma triglyceride and LDL-cholesterol with improved HbA_{1c} in Type 2 DM.[20] In the Diabetes Control and Complications Trial (DCCT), there was a 41 % reduction in the incidence of CVD in the intensively treated group (HbA_{1c} 7 %) compared with the conventionally treated group (HbA_{1c} 9 %), although this did not reach statistical significance.[21] Similar results were also found in Japanese Type 2 DM patients, in a similarly designed study. In the conventionally treated group (HbA_{1c} 9.4 %), the incidence of CVD was 1.3 events per 100 patient-years compared to 0.6 events per 100 patient-years in an intensively treated group (HbA_{1c} 7.1 %) although this again fell short of significance.[22] In a more recent study, tight glycaemic control was associated with decreased mortality following myocardial infarction.[6]

A continuous relationship has been observed between the risk of CVD and raised postprandial glucose concentrations that ranged from barely elevated values to diabetic levels.[23] The increased risk of CVD is well recognized in subjects with newly diagnosed Type 2 DM or IGT,[24–26] suggesting that the process of atherogenesis may have already begun to accelerate before abnormal glucose tolerance had developed. Against this background, the term dysglycaemia has been recently introduced to define the range of blood glucose associated with increased CVD risk.[9] However, the inherent variability of blood glucose concentrations often makes interpretation of a single blood glucose difficult and HbA_{1c} may be a more useful index to reflect chronic hyperglycaemia.[13] In the present analysis, we found significant associations between HbA_{1c} and CVD risk factors including blood pressure, central adiposity, plasma glucose, 2-h plasma insulin, lipid parameters, and urate concentrations in subjects with normal glucose tolerance. Some of the associations were explained by differences in age and sex. However, even after adjustment for age and sex, HbA_{1c} was still closely associated with fasting and 2-h plasma glucose, 2-h plasma insulin, total cholesterol, and low-density lipoprotein cholesterol concentrations.

Type 2 DM is now recognized to be part of a multifaceted syndrome involving ageing, hyperlipidaemia, hyperinsulinaemia, hypertension, and microalbuminuria.[27] Although hyperinsulinaemia is often referred to as a possible linking factor for this multi-faceted syndrome,[27] this proposition remains controversial since the relationships are not always upheld in clinical studies.[28] The application of structured equation modelling using data obtained from the same study as reported here suggests the centrality of ageing, obesity, and family history rather than insulin in the causation of the Metabolic Syndrome.[29] In the present study, HbA_{1c} was positively associated with the 2-h but not with the fasting insulin concentrations. So increasing HbA_{1c} level may be positively associated with insulin resistance even when the HbA_{1c} is within the non-diabetic range. More study is required in this area. It is interesting to note that men had higher HbA_{1c} but lower fasting and 2-h plasma glucose than women. The differences were partly explained by younger age and higher haemoglobin concentrations in men. However, this also raises the possibility that associations between HbA_{1c} and certain cardiovascular risk factors may not be due to glycaemic status alone.

In conclusion, in this population-based study, we found close associations between HbA_{1c} and certain CVD risk factors, notably fasting and 2-h plasma glucose, 2-h plasma insulin, plasma cholesterol, and low-density lipoprotein. The relationships cannot be explained entirely by age or sex. These findings emphasize the importance of examining hyperglycaemia, as reflected by HbA_{1c}, as a continuum in the evaluation of cardiovascular risk.

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